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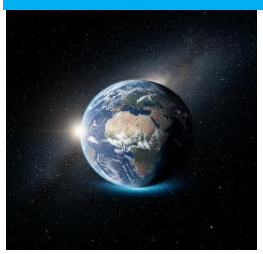

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Effects of Exercise on Inflammatory Biomarkers in Rheumatoid Arthritis

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Abstract

Background

Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by persistent synovial inflammation leading to joint destruction, disability, and increased cardiovascular risk. Exercise is increasingly recognized as a non-pharmacological therapy that may modulate inflammation and improve clinical outcomes in RA.

Aim

The aim of this review was to evaluate the effects of different exercise modalities on inflammatory biomarkers in individuals with RA.

Material and methods

A narrative review was conducted using studies published in peer-reviewed journals, identified through databases such as PubMed. Randomized controlled trials, clinical interventions, and systematic reviews assessing the impact of aerobic, resistance, and combined training on inflammatory markers in adults with RA were included. Data were extracted on exercise protocols, biomarker outcomes, and methodological quality.

Results:

Exercise interventions in RA show variable effects on inflammatory biomarkers. Aerobic training consistently reduces CRP and TNF-α, while effects on IL-6 and ESR are less consistent. Resistance training primarily lowers ESR and CRP, with transient changes in interleukins. Combined aerobic and resistance programs demonstrate the broadest anti-inflammatory impact, reducing CRP and IL-6, modulating regulatory T and B cells, and improving disease activity and quality of life. Short-term, moderate-intensity, and home-based interventions are safe and effective, whereas low-intensity exercise shows limited biomarker changes.

Conclusions:

Regular exercise is safe and beneficial for patients with RA, reducing disease activity, improving physical function, and modulating inflammatory biomarkers, particularly CRP and IL-6. Combined aerobic and resistance training offers the broadest anti-inflammatory and clinical benefits. Further research is needed to determine the most effective interventions for targeted modulation of inflammation.

Key words: Rheumatoid arthritis, exercise, inflammation, C-reactive protein, ESR, cytokines, aerobic training, resistance training.

Introduction

Rheumatoid arthritis (RA) is a chronic, autoimmune inflammatory disease that leads to joint pain, stiffness, swelling, and progressive disability. In 2020, approximately 17.6 million people worldwide were living with RA, with an incidence rate of 208.8 cases per 100.000 population. Women are affected about 2.5 times more often than men. The disease was responsibile for 3.06 DALYs, with 76 percent of years lived with disability, mainly due to chronic pain and functional limitations. From 1990 to 2020, the disability burden rose by over 13 percent, and by 2050 the number of people living with RA may reach 31.7 million. [1]

Patients with RA show significantly higher levels of physical inactivity. As many as 42 percent of adults with the condition do not engage in any 10-minute bout of moderate or vigorous physical activity during the week, due in part to pain, fatigue, and low motivation. [2] A sedentary lifestyle contributes to the development of rheumatoid cachexia, characterized by loss of muscle mass alongside an increase in fat tissue, which leads to reduced muscle strength and impaired function. [3] In addition, patients have a higher risk of osteoporosis and fractures. Osteoporosis is found in 30-50 percent of them.[4] The risk of fractures is twice as high as in the general population. Low physical activity also worsens cardiorespiratory and metabolic fitness, contributing to increased cardiovascular risk and lowering quality of life.[5]

Regular physical activity, including activities such as walking or household chores, can improve patients' functional abilities and help reduce disease activity. [6] Beyond pharmacological treatment, it plays an important role due to its anti-inflammatory effects.

In rheumatoid arthritis (RA), the disease process is driven by the production of autoantibodies, such as RF and ACPA. They trigger an immune response that leads to the release of pro-inflammatory cytokines like TNF-α, IL-6, IL-1β, and GM-CSF.[7] These cytokines are key targets for modern biologic therapies.[8] CRP, ESR, and cytokines are routinely measured to monitor inflammatory activity and assess the effectiveness of therapy.[9]

An increasing number of studies suggest that physical activity, especially when regular and properly planned, can help lower levels of pro-inflammatory markers in the blood.[10] Unlike pharmacological treatments, exercise is a safe, non-drug approach that can positively influence multiple aspects of health in people with RA. [11]

The aim of this review is to evaluate how different forms of physical activity - namely aerobic, resistance and combined training - affect inflammatory processes in people with RA. Changes in key inflammatory biomarkers (TNF- α, IL-6, IL-1β, CRP) are discussed in relation to the intensity and frequency of exercise. The review also highlights the limitations of existing studies and outlines directions for future research needed to optimize physical activity recommendations as an adjunct therapy for patients with RA.

Based on the available literature, it remains unclear how different types of physical activity affect inflammatory markers in patients with RA. There is also a lack of clear data on the relationship between exercise intensity and frequency and changes in TNF-α, IL-6, IL-1β and CRP levels. Another challenge is the high heterogeneity of studies, which makes it difficult to develop practical exercise recommendations.

Regular physical activity is believed to reduce levels of key pro-inflammatory cytokines as well as CRP in people with RA. It is also suggested that different types of exercise may have varying anti-inflammatory effects with higher intensity workouts potentially producing a stronger biological response.

Pathophysiology of Inflammation in RA

The immune system in rheumatoid arthritis doesn't just malfunction. It becomes the driving force behind the damage. Disturbances in adaptive immunity play a central role: B and T lymphocytes trigger a cascade of inflammatory cytokines, fibroblasts become activated, and together these processes fuel synovial inflammation and joint destruction.[12]

There is strong evidence that autoreactive CD4+ helper T cells play a major role in RA. For example, most animal models do not develop joint inflammation without these cells. They infiltrate the synovial membrane in large numbers and become activated there. [13]

Dendritic cells (DCs) present autoantigens and provide naive T cells with costimulatory signals guiding their differentiation. In RA, this interaction between DCs and T cells is disrupted, leading to the generation of proinflammatory T cell subtypes. [22]

In response to cytokine signals, CD4+ T cells differentiate into distinct subpopulations. Th1 cells promote inflammation, mainly through IFN-gamma and TNF-α. Th17 cells are crucial in autoimmune diseases and produce cytokines such as IL-17, IL-6 and GM-CSF. Th2 cells help regulate the humoral immune response, while Tfh cells support B cell activation and the production of autoantibodies. [14]

Historically, Th1 and Th17 helper T cells were thought to be the main pathogenic cells in RA-affected joints. However, current evidence does not fully support this idea, making it difficult to pinpoint which exact T helper cell subtype drives joint inflammation. [13] Other subpopulations include Th9 cells, whose development depends on TGF-β and IL-4, and Treg cells, which help maintain immune tolerance. [14]

A key feature in RA pathogenesis is the lack of immune tolerance. Regulatory T cells (Treg), which normally suppress autoreactive effector T cells, are reduced in number or functionally impaired in RA. Similarly, regulatory B cells (Breg), which produce anti-inflammatory cytokines such as IL-10, TGF-β and IL-35, are less abundant and unable to control excessive lymphocyte activation. Together, these disruptions in immune regulation contribute to persistent autoimmunity and chronic inflammation. [14,17]

Atypical T cell subpopulations, such as γδ T cells, NKT cells and MAIT cells, also contribute to RA pathogenesis. They bridge innate and adaptive immunity, support cytokine production, and contribute to tissue damage. [15]

B cells contribute to RA pathogenesis in many ways. They produce autoantibodies like RF and ACPA that drive joint inflammation. They act as antigen-presenting cells, activating T cells and producing inflammatory cytokines (TNF-α, IL-6, IL-12, IL-23, IL-1α). [16]

Proinflammatory cytokines create a positive feedback loop, amplifying inflammation. [18] TNF, IL-1, and IL-6 stimulate fibroblast-like synoviocytes (FLS) and macrophages to release more inflammatory mediators, driving synovial hyperplasia and pannus formation. [21] Activated FLS produce matrix metalloproteinases and RANKL, which promote osteoclast formation and lead to cartilage and bone destruction. [20]

Studies on targeted therapies in RA show that specific cytokines play dominant roles in different stages of the disease. [19]

Biomarkers of disease activity

Assessing rheumatoid arthritis (RA) activity relies on a combination of clinical observation and analysis of biological markers that reflect the level of inflammation, autoimmunity, and tissue damage. [23] The most commonly used markers include CRP, ESR, IL-6, TNF-α, autoantibodies, and matrix metalloproteinases (MMPs).

C-reactive protein is an acute-phase protein produced by the liver in response to interleukin-6 (IL-6). Its levels rise quickly during active inflammation and decrease after effective treatment. Elevated CRP correlates with disease activity score (DAS28, SDAI) and can help predict the progression of radiographic changes. [24]

The erythrocyte sedimentation rate (ESR) measures how quickly red blood cells settle in a blood sample. The faster they settle, the more intense the inflammation usually is. Factors such as fibrinogen levels and antibodies can influence ESR results. [25]

Although ESR is less precise than CRP and responds more slowly to changes during treatment, it remains a useful marker in routine diagnostics and clinical studies. [26] Recent data confirm that both CRP and ESR show a moderate correlation with disease activity, although in up to 40% of RA patients, their levels may remain within the normal range. [25,27]

Interleukin-6 (IL-6) is a pleiotropic cytokine that induces the production of CRP, SAA, fibrinogen, haptoglobin, and α1-antichymotrypsin. Under normal conditions, it is produced briefly in response to infection or tissue injury, activating defense mechanisms. Its signaling

subsides once the stimulus is removed. In rheumatoid arthritis this regulation is disrupted. [28] Elevated IL-6 levels serve as a marker of inflammation in RA patients and can help predict symptom severity, including pain, fatigue, and depression, as well as the treatment response. [29]

TNF-α, mainly released by macrophages and synovial fibroblasts, is a major driver of chronic joint inflammation in most RA patients. It increases adhesion molecules, chemokines, and MMPs, which intensify inflammation. [30,31] The effectiveness of TNF-α inhibitors (adalimumab, infliximab, etanercept) confirms its key role in disease pathogenesis and its clinical significance as a biomarker. [32]

Other characteristic markers of RA are rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA). ACPA is more specific to RA than RF, so it is often tested in patients suspected of having the disease. Both RF and ACPA can indicate a higher risk of rapid disease progression, severe symptoms outside the joints, and increased mortality. Patients who are seropositive often respond better to certain targeted treatments, especially rituximab, and using abatacept in ACPA-positive patients may help delay or even prevent the onset of RA. [33]

In some individuals who will later develop rheumatoid arthritis (RA), autoantibodies - particularly ACPA - can appear in the blood many years before clinical symptoms arise. [34] RF and ACPA form immune complexes that activate the complement system, sustaining inflammation. [34,35] The levels of these antibodies usually do not fluctuate with short-term changes in disease activity, which limits their usefulness as dynamic markers of treatment response. [36]

Among matrix metalloproteinases (MMPs), MMP-3 (stromelysin-1) has been studied most extensively in RA. It is produced by synovial fibroblasts and B cells and contributes to cartilage destruction and the growth of inflamed synovial tissue. Serum MMP-3 levels correlate with the severity of joint damage and can decrease in response to effective treatment, making it a potential biomarker of tissue injury and repair. [25]

These biomarkers show different, though partially overlapping, aspects of RA: from systemic inflammation (CRP, ESR) to cytokine activity (IL-6, TNF-α), autoimmune responses (RF, ACPA), and cartilage degradation and tissue remodeling (MMP-3). Traditional markers remain the cornerstone of evaluating disease progression, but the growing use of molecular markers allows a deeper understanding of RA development and treatment response. This is particularly relevant for studies investigating physical activity as a potential strategy to reduce inflammation.

Chronic inflammation and systemic consequences

Chronic inflammation in rheumatoid arthritis (RA) is not limited to joint damage; it also leads to various systemic effects, including an increased risk of cardiovascular disease, persistent fatigue, and loss of muscle mass and strength (sarcopenia) [37,38].

People with RA are at higher risk of developing atherosclerosis and heart failure, even in the absence of traditional risk factors. Chronic inflammation affects blood vessels and disrupts lipid metabolism. Higher levels of markers like CRP, ESR, IL-6, and TNF-α are linked to greater chances of cardiovascular death. Keeping disease activity under control, especially with modern anti-inflammatory treatments, can lower the risk of heart and blood vessel problems. [39,40]

Fatigue is one of the most commonly reported symptoms in RA and often persists even when joint inflammation is well controlled. Proinflammatory cytokines are thought to play a key role in causing these disease-related symptoms, including fatigue. [41]

Sarcopenia is common in RA. Depending on the criteria, it affects 24-30% of patients. Some studies report sarcopenia in up to 60% of patients. [37,42]

Mechanisms of sarcopenia include chronic cytokine activity (IL-6, TNF-α, IL-1β) that shifts the balance toward catabolism, reduced physical activity due to pain and stiffness, and side effects of treatment (for example, glucocorticoids). Sarcopenia in RA is associated with poorer clinical outcomes: greater disability, higher fracture risk, reduced quality of life, and potentially an increased risk of cardiovascular disease. [37]

Exercise as an anti-inflammatory intervention

Regular exercise plays a key role in improving joint function in patients with rheumatoid arthritis. By strengthening the muscles surrounding joints, increasing range of motion, and stimulating the circulatory system, physical activity reduces pain and morning stiffness. [43]

Exercise improves muscle endurance and strength, which translates into better joint stabilization, greater efficiency in daily activities, and reduced progressive loss of motor function. [44] Long-term regular training is therefore not only a complement to pharmacological therapy but also a key element in preventing complications and maintaining quality of life.

Physical activity influences inflammation through several interrelated mechanisms, including myokine release by muscles, modulation of adipose tissue and adipokines, and short-term hormonal responses that regulate immune function. [45] Contracting skeletal muscles secrete numerous signaling molecules (myokines) that act both locally and systemically. [46]

One of the best-known examples is interleukin-6 (IL-6). Its levels increase dramatically during exercise, but in this context, it primarily serves an anti-inflammatory function. It stimulates the production of IL-10 and the IL-1 receptor antagonist. It also inhibits the production of TNF-α. [47,48] Regular training shifts the cytokine balance toward anti-inflammatory effects in both the short and long term. Other exercise-induced myokines, such as IL-15, also participate in immune regulation. [49]

IL-10, whose expression increases in response to IL-6 released during exercise, promotes the transformation of macrophages into the M2 (reparative) phenotype in both peripheral tissues and systemic circulation and inhibits pro-inflammatory signaling.[50-52,56] This process helps reduce inflammation, supports tissue repair, and is considered one of the key immunoregulatory mechanisms associated with physical activity. The increased IL-10 to TNF-α ratio after training is considered one of the mechanisms by which physical activity reduces systemic inflammation. [53]

Regular exercise goes beyond local effects in skeletal muscle; it also affects immune cell function throughout the body. Exercise modulates T and B cell activity, promoting a balance between pro-inflammatory and regulatory subtypes, which may limit excessive immune responses. [54, 55]

Adipose tissue isn't merely a passive energy store; it actively influences the immune system. [57,58] People with RA are more likely to have visceral obesity, and this type of fat has a particularly negative effect: it stimulates the immune system to maintain inflammation and contributes to a worsening course of the disease. [59,60] Fat cells produce signals called adipokines (including leptin, adiponectin, and resistin), which can either increase inflammation or help calm it, depending on the ratio.[61] When the former predominates, the body remains in "alarm mode". Regular exercise reduces visceral fat and improves adipokine balance, leading to an anti-inflammatory effect. [62] As a result, exercise not only strengthens muscles and improves mood, but also significantly reduces one of the important extra-articular "generators" of inflammation in RA.

Types and intensity of exercise

Treatment of rheumatoid arthritis (RA) involves various forms of physical activity that affect joint function, muscle mass, and inflammation.[3] Aerobic exercise, such as walking, cycling, or swimming, primarily improves cardiorespiratory fitness, joint mobility, and overall physical fitness, while also having a moderate anti-inflammatory effect. [44] Resistance (strength)

exercises focus on strengthening the muscles surrounding joints, improving stabilization, range of motion, and limiting progressive loss of muscle function. [43] In practice, combining both types of training is often recommended, creating programs that simultaneously improve endurance and muscle strength.[63] For safe and effective exercise in RA, moderate-intensity sessions of 30–60 minutes, 2–4 times per week, including recovery days and monitoring for joint pain or swelling, are recommended. [64]

Clinical trials and systematic reviews indicate that both aerobic and strength training can reduce pain, improve daily activity comfort, and increase range of motion in affected joints. [43,65] These effects are mediated by strengthening muscles around the joints, modulating tissue blood supply, and altering inflammatory responses. [66,67] Studies in patients with RA have shown that exercise programs lead to short-term improvements in pain scores and morning stiffness, and that regular physical activity maintains these benefits in the long term. [63]

Although beneficial for RA patients, exercise may need to be modified or limited in certain situations. [68] The main contraindications include periods of disease exacerbation, the presence of active inflammation in the joints, severe pain, swelling or significant joint instability. [69]

Regular, long-term physical activity provides many benefits to patients with rheumatoid arthritis (RA) that go beyond improving joint function.[70] Regular exercise reduces the risk of cardiovascular disease, which is increased in RA due to chronic inflammation.[71] They improve bone mineral density, which prevents osteoporosis, and help maintain muscle mass and strength, limiting the development of sarcopenia. [72,73] Moreover, physical activity positively impacts mental health by reducing stress and depression and enhances quality of life by increasing independence in daily activities and overall fitness. [74]

Regular trening in patients with RA improves joint function, strengthens muscles, increases range of motion, and reduces pain and stiffness. It also has anti-inflammatory effects by modulating the immune system and adipokine balance, providing benefits both locally and systemically. Sustained exercise supports cardiovascular, bone, and muscle health, as well as improving well-being and quality of life. It is crucial to tailor each training program to the patient’s individual condition.

Effects of exercise on inflammatory biomarkers

Recently, researchers have become increasingly interested in how exercise affects inflammatory biomarkers in RA patients, in addition to its established benefits on symptoms

and physical function. Exercise is effective at easing pain, fatigue, and overall disease activity (DAS28), but its impact on biomarkers such as CRP, ESR, IL-6, and TNF-α remains unclear, with research findings varying across studies.

Short-term physical exercise does not exacerbate symptoms or inflammatory processes, levels of CRP, ESR, and proinflammatory cytokines (IL-6, TNF-α) remain stable after single exercise sessions, dispelling concerns about "exercise-induced disease flares" and supporting the introduction of physical activity early in treatment.[3,79] In contrast, individualized exercise programs, monitored regularly (e.g., every three months), can lead to reductions in CRP and ESR, along with improvements in quality of life, physical capacity, and cognitive function.[75–78] The anti-inflammatory effects of exercise likely arise primarily from indirect mechanisms such as enhanced metabolism, reduced oxidative stress, improved neuroendocrine regulation, and alleviation of pain and fatigue, rather than from direct modulation of cytokine levels.[77]

Studies on aerobic training have shown that aerobic exercise can influence selected inflammatory biomarkers in rheumatoid arthritis, although the effects are not uniform across all markers. The most consistently observed outcome is a reduction in CRP, as demonstrated both in an interventional study where the exercise group experienced a significant decrease in CRP compared to controls [80], and in an analysis showing that aerobic exercise is among the forms of activity associated with CRP reduction in populations with chronic diseases [87]. The same analysis also showed that aerobic training alone led to a significant drop in TNF-α, suggesting that aerobic exercise may help control the proinflammatory response by influencing key cytokines involved in chronic inflammation [87]. One possible explanation is that exercise triggers the release of anti-inflammatory myokines, such as IL-6, and reduces visceral fat, a key contributor to TNF-α production [47]. In people with RA, a single session of aerobic exercise raises IL-6 levels. This likely reflects a beneficial, muscle-driven response with anti-inflammatory effects, even though IL-6 is already elevated at baseline. In healthy individuals the same exercise did not result in any change in IL-6, and no such increase was observed. [88] Evidence for a stable impact of aerobic exercise on ESR is limited, as this marker was not consistently altered in interventions consisting only of aerobic activity. Studies have also reported decreases in fibrinogen levels and leukocyte counts, further supporting the anti-inflammatory benefits of aerobic activity in this population [3,75]. This is supported by a meta-analysis of 13 randomized trials with 967 participants, which found aerobic training to be safe and effective.[43] Although this analysis did not focus directly on TNF-α or IL-6 levels, the

observed clinical improvements suggest that aerobic exercise contributes to lowering inflammation and disease activity, reinforcing its role as a safe adjunctive therapy in RA management. Aerobic exercise reliably lowers CRP and TNF-α, while its impact on other interleukins can vary based on the exercise program and the participants involved.

Resistance training tends to have more consistent effects, especially in reducing the markers commonly used to track inflammation in RA. The most robust and clear effect is seen for ESR, which showed a significant decrease (SMD −0.86) in a large meta-analysis of 17 RCTs, confirming that resistance exercise can effectively modulate inflammatory activity as measured by classic laboratory markers [81]. A broad analysis also showed that resistance training can reduce CRP, suggesting that even short, moderate-intensity strength sessions may help improve systemic inflammation [87]. A study examining the acute response to exercise found that IL-1β, IL-1ra, IL-10, and IL-6 levels changed immediately afterward, but these effects were temporary and did not reflect lasting modulation of inflammation, while TNF-α and CRP remained unchanged [86]. Broader analyses, including 1,128 participants, indicate that isokinetic exercise reduces CRP, IL-6, and TNF-α, highlighting a more universal anti-inflammatory effect that may complement biologic therapy [10]. Regular resistance training, as well as combined moderate-intensity aerobic and resistance exercise, effectively reduces CRP and ESR, enhances IL-10 levels and immune function (Treg/Breg), while also alleviating fatigue and improving quality of life.[75-81] However, the direction and magnitude of these changes may depend on factors such as age, training intensity, and program duration; for example, in older participants, some studies observed a reduction in Treg and Breg counts without any increase in disease activity or inflammatory markers [83]. In general, resistance training primarily lowers ESR and CRP, whereas changes in interleukins appear transient, likely representing a short-term physiological reaction rather than long-term modulation of cytokines. A meta-analysis showed that combined training leads to the most consistent and clear reduction in IL-6, setting it apart from purely aerobic or purely resistance protocols, which did not yield such uniform results [87]. At the same time, combined training also lowered CRP, a finding supported both by the review [87] and by an interventional study showing reduced CRP compared with controls [80]. Another 20-week program found no change in CRP but did show a significant reduction in regulatory T and B cells (Treg and Breg) [83], suggesting that combined training may influence inflammation by altering lymphocyte populations, even when standard markers like CRP stay the same. Its impact on ESR remains uncertain, with available

studies failing to show consistent decreases [80, 83, 87]. Overall, combined training seems to have the widest anti-inflammatory effect, lowering IL-6 and CRP while also affecting important immune regulators, making it the most versatile approach for modulating inflammation.

Short-term and home-based interventions carried out at moderate intensity, including programs that combine resistance exercise with occupational therapy, have also been shown to improve DAS28, CRP, and both physical and psychological functioning [84]. High-intensity combined training (HIIT plus resistance exercise) produced additional benefits, reducing fatigue, pain, and overall disease activity, while mechanistic analyses showed decreases in IL-6 and TNF-α [87].

Long-term high-intensity exercise programs, such as the two-year RAPIT trial, improved physical function and overall wellbeing without increasing CRP or DAS28, confirming that well-controlled patients can safely engage in intensive training [85]. In contrast, low-intensity exercise performed for eight weeks did not trigger any anti-inflammatory adaptations, and in some cases CRP and RF even increased [75].

In summary, different forms of exercise influence inflammation through distinct pathways, ranging from better circulation to reduced oxidative stress and shifts in cytokine and regulatory cell activity. Combining aerobic and resistance training appears to be the most effective approach for lowering CRP, IL-6, and overall disease activity (DAS28), making it a solid complementary strategy alongside pharmacological treatment in RA [63].

Discussion

Current literature shows a clear research gap when it comes to direct comparisons between aerobic, resistance, and combined training in terms of their effects on inflammatory markers in patients with RA. There are still very few studies that directly compare these types of exercise, especially when it comes to important biomarkers like CRP, IL-6, and TNF-α. Without direct comparisons, it’s hard to know which type of exercise is most effective at controlling inflammation.

Evidence from clinical trials and meta-analyses indicates that regular exercise is safe for RA patients and can influence inflammation, both indirectly through better clinical outcomes and directly by modulating inflammatory biomarkers. Aerobic, resistance, and combined training have all been shown to reduce disease activity (DAS28), improve physical function, and

decrease fatigue, and most studies report no increase in proinflammatory cytokines in response to exercise [43,75,79–83]. Many analyses also note moderate reductions in ESR and CRP, suggesting that the anti-inflammatory effects of exercise are driven largely by improvements in metabolism, reductions in visceral adiposity, and better regulation of the neuroendocrine system [77,78].

Resistance and combined training improve muscle strength, help counteract sarcopenia, and reduce cardiovascular risk, while also exerting beneficial effects on inflammatory markers without worsening disease symptoms [3,81,85]. These benefits may persist even after the intervention ends, provided that physical activity is maintained [87]. Regular, individually tailored exercise is an important component of adjunct therapy in RA, combining improvements in physical function with immunomodulatory effects.

The way exercise affects the body can differ depending on the type of activity. Aerobic exercise enhances endothelial function, reduces oxidative stress, and increases tissue insulin sensitivity, which indirectly contributes to lowering pro-inflammatory cytokines [43,75,89]. Resistance training induces adaptations in skeletal muscles, boosting the release of anti-inflammatory myokines (including IL-6 in its anti-inflammatory role, IL-10, and IL-1ra) [47,50,75]. Combined programs, which integrate both aerobic and resistance components, often produce the greatest reductions in inflammatory markers and the most significant improvements in quality of life [76,81,87].

Despite consistent evidence highlighting the safety and benefits of physical activity in RA, the available studies are highly heterogeneous. Differences exist in patient populations, types and intensities of exercise, duration of interventions, and methods used to assess biomarkers. Many analyses involve small sample sizes and short follow-up periods, making it difficult to evaluate the long-term stability of inflammatory markers [77,81]. Some studies also fail to control for key confounding factors, such as diet, body composition, or physical activity outside the intervention. Furthermore, there is a lack of in-depth research examining the molecular mechanisms of exercise-induced adaptations in patients receiving biologic therapies. Taken together, these gaps show how important it is to conduct more comparative research on how aerobic, resistance, and combined exercise influence inflammatory markers.

Conclusions

Regular exercise is a safe and effective addition to treatment for people with rheumatoid arthritis. Aerobic, resistance, and combined training can all help improve physical function,

quality of life, and overall well-being, without worsening disease symptoms or inflammation. Current evidence suggests that exercise has a modest but meaningful anti-inflammatory effect, mainly through indirect pathways like improved metabolism, reduced visceral fat, lower oxidative stress, and positive effects on the neuroendocrine system.

Training that combines aerobic and resistance exercises appears to be the most effective for reducing inflammation and enhancing overall physical function. Consistency and individualized adjustment of exercise intensity are key to maintaining long-term benefits and minimizing the risk of disease flares.

Future studies should include larger patient populations, longer follow-up periods, and detailed assessments of immune responses according to the type of exercise and biologic therapy. Understanding how exercise influences the immune system at a molecular level can help us provide clearer guidance on including physical activity in the care of people with RA.

Disclosures

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